PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*)	28 JAN 2008
Applicant's or agent's file reference B0801.70327	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US07/03160	05 February 2007 (05.02.2007)	06 February 2006 (06.02.2006)

International Patent Classification (IPC) or both national classification and IPC

IPC: C12Q 1/68(2006.01);A61K 39/00(2006.01);A61K 39/38(2006.01)
USPC: 424/184.1

Applicant

THE BRIGHAM AND WOMEN'S HOSPITAL, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☒ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	27 December 2007 (27.12.2007)	Maury Audet Telephone No. 571-272-1600

Form PCT/ISA/237 (cover sheet) (April 2005)

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Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ on paper

☐ in electronic form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 10-32

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 10-32

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
   - ☐ paid additional fees
   - ☐ paid additional fees under protest and, where applicable, the protest fee
   - ☐ paid additional fees under protest but the applicable protest fee was not paid
   - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
   - ☐ complied with
   - ☒ not complied with for the following reasons:

   See the lack of unity section of the International Search Report(Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:
   - ☐ all parts.
   - ☒ the parts relating to claims Nos. 1-9

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Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims NONE	YES
	Claims 1-9	NO
Inventive step (IS)	Claims NONE	YES
	Claims 1-9	NO
Industrial applicability (IA)	Claims 1-9	YES
	Claims NONE	NO

2. Citations and explanations:

Claims 1-9 lack novelty under PCT Article 33(2) as being anticipated by Tzianabos et al. (US 2004/0219160 A1).

The claims are broadly drawn to a nutritional formula or nutritional supplement composition comprising an isolated zwitterionic polysaccharide consisting essentially of repeating units which comprises two to ten monosaccharides and a free amino moiety and a negatively charged moiety selected from the group consisting of carboxylate, phosphate, phosphonate, sulfate and sulfonate wherein the zwitterionic polysaccharide is a *Bacteroides fragilis* polysaccharides A (PSA).

Tzianabos et al. teach a pharmaceutical composition comprising a polymer of repeating units of a charge motif characteristic of *Bacteroides fragilis* polysaccharides A (PSA), the motif being a positively charged free amino moiety and a negatively charged moiety selected from the group consisting of carboxylate, phosphate, phosphonate, sulfate and sulfonate (see column 24, claim 73). The cited art further teaches that the polymer used in the composition can be a polysaccharide formed of repeating units of a maximum of ten monosaccharides wherein each repeating unit includes at least one free amino acid moiety and a negatively charged moiety selected from the group consisting of carboxylate, phosphate, phosphonate, sulfate and sulfonate and wherein such polysaccharides occur in nature and can be isolated (see column 15, paragraph 0165). The cited art further teaches about zwitterrionic polysaccharide A1 (PSA1), polysaccharide A2 (PSA2), polysaccharide B (PSB) [see column 23, claims 7-9] and also teaches about the selection of zwitterionic polysaccharides from the group consisting of *Shigella sonnei* Phase I lipopolysaccharide O-antigen, *Streptococcus pneumoniae* type I capsular polysaccharides and'Streptococcus pneumoniae group antigen C substance (see column 16, paragraph 0180). Thus, Tzianabos et al anticipates the invention as claimed.

Claims 1-9 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

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Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

VIII. The following observations on the clarity of the claims, description, and drawings or on the questions, are made:
Claims 1, 8-9 are objected under PCT Rule 66.2 9(a)(v) as lacking clarity under PCT Article 6 because claims 1, 8-9 are indefinite for the following reasons: The terms "nutritional formula" and "nutritional supplement" and "consisting essentially of repeating units" are not recognized and fail to clearly set forth the metes and bounds of the invention. It is unclear from the description what applicant intends these terms to mean.

Claims 1-9 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because of the claims 1-9 are not fully supported by the description. The description does not disclose the claimed invention in a manner sufficiently clear and complete for the claimed invention to be carried out by a person skilled in the art because:

The claims are broadly drawn to a nutritional formula or nutritional supplement composition comprising an isolated zwitterionic polysaccharide consisting essentially of repeating units which comprises two to ten monosaccharides and a free amino moiety and a negatively charged moiety selected from the group consisting of carboxylate, phosphate, phosphonate, sulfate and sulfonate wherein the zwitterionic polysaccharide is a *Bacteroides fragilis* polysaccharides A (PSA)

The description while enabling a nutritional formula or nutritional supplement composition comprising an isolated zwitterionic polysaccharide does not reasonably provide enablement for repeating units and molecular weight of different species of zwitterionic polysaccharide. The description does not enable any person skilled in the art to which it pertains, or with which it is more nearly connected, to make and use the invention commensurate in scope with these claims.

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Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

The description at page 11 says that the zwitterionic polysaccharides useful according to the invention generally have a plurality of repeating units, wherein each repeating unit comprises two to ten monosaccharide and a positively charged free amino moiety and a negatively charged moiety selected from the group consisting of carboxylate, phosphate, phosphonate, sulfate and sulfonate. The description further says that molecular weight of the zwitterionic polysaccharides useful in the invention typically have molecular weights between 500 Da and 2,000,000 Da. However, there is no amount of guidance in the description as to how many repeating units of zwitterionic polysaccharides are required to elicit T cell dependent immune response (e.g. Th 1/Th 2 balance for the host). Further, the different species of polysaccharides are claimed in the invention but no amount of guidance is given guidance in the description as to effect of their molecular size in stimulation of cellular immunity. The using of zwitterionic polysaccharides with molecular weight less than 5000 Da for stimulation of cellular immunity is highly unpredictable. Kalka-Moll et al (Effect of molecular size on the ability of zwitterionic polysaccharides to stimulate cellular immunity, *The Journal of Immunology*, 2000, 164: 719-724) teach that the molecular size of zwitterionic polysaccharides affects their ability to stimulate cellular immunity. PS A with average molecular sizes of 129.0 (native), 77.8, 46.9, and 17.1 kDa stimulated $CD4^+$ cell proliferation *in vitro* to the same degree, whereas the 5.0 kDa fragment was much less stimulatory. The reference further teaches that a zwitterionic polysaccharide as small as 22 repeating units (88 monosaccharide) are required to elicits a T cell dependent immune response (see especially abstract and title).

Therefore, in the instant disclosure the quantity of experimentation would be very high because of unspecified number of repeating units of the zwitterionic polysaccharides and using of zwitterionic polysaccharides with molecular weights between 500 Da and 2,000,000 Da when the reference as cited above teaches that the fragment of 5000 Da would not work as it could be much less stimulatory. Owing to this, it would require an undue burden of experimentation for a skilled artisan to determine the zwitterionic polysaccharide with particular number of repeating units and molecular weight.

There are no working examples in the description which drawn to support the use of isolated PSA 1, PSA 2 and PSB in the composition as claimed. There is no guidance in the description as to how these different species of zwitterioninc polysaccharides can be isolated. Further there is absolutely no support in the description as to how "nutritional formula" or "nutritional supplement" comprising isolated zwitterioninc polysaccharides can be made. There is no specific direction or guidance as to a regimen or dosage effective specifically against certain deficiency in particular patient population. It is well known in the art and admitted by the applicant at page 3 of the specification that administration of a zwitterioninc polysaccharide such as the bacterial capsular polysaccharide isolated from *B. fragilis* can influence immune homeostasis. Hence terms "nutritional formula" and "nutritional supplement" are appears to very vague, unclear and not enabled to a one of ordinary person skilled in the art.

Given the breadth of the claim, lack of guidance and unpredictability as set forth above, undue experimentation would have been required by one of ordinary person skill in the art to practice the claimed invention.